



C–H activation by immobilized heterogeneous photocatalysts

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Abstract

During the last decades, the merger of photocatalysis with transition metal chemistry has been surfaced as a sustainable tool in modern molecular syntheses. This Account highlights major advances in synergistic photo-enabled C–H activations. Inspired by our homogenous ruthenium- and copper-catalyzed C–H activations in the absence of an exogenous photosensitizer, this Account describes the recent progress on heterogeneous photo-induced C–H activation enabled by immobilized hybrid catalysts until September 2021, with a topical focus on recyclability as well as robustness of the heterogeneous photocatalyst.

1 Introduction

The tremendous progress achieved in molecular syntheses during the last decade has resulted in a significant improvement of the organic chemistry. Thus, modern organic synthesis is the key to the development of structural complexity, including the transformation of hydrocarbons to useful and high-valued compounds by straightforward and sustainable methods. While the development of metal-catalyzed cross-coupling reactions had resulted in significant advances [1, 2], major drawbacks continued to limit this approach, such as the pre-functionalization of starting materials and stoichiometric waste production. In stark contrast, the direct activation of omnipresent C–H bonds emerged as a transformative tool [3, 4] for the step-economical and sustainable approach [5–7] not only towards organic chemistry, but indeed also applied areas, such as drug discovery, crop protection, and materials science (Fig. 1a) [8–11].

Photocatalysis has recently been identified as an increasingly powerful technique in sustainable organic syntheses. In 2007, a pioneering report by Osawa [12], merging photocatalysis with transition metal-catalyzed reactions (Fig. 1b), unlocked a dormant area of photocatalysis [13, 14]. In sharp

contrast, Ackermann [15–17] and later Greaney [18, 19] elegantly disclosed C–H activation by ruthenaphotoredox catalysis under exogenous-photosensitizer-free conditions. While C–H activation has predominantly exploited noble 4d or 5d transition metals, the introduction of Earth-abundant and cost-effective 3d metal catalysts [20–23], particularly copper and cobalt, allows for more sustainable and photo-induced C–H activation. In this context, Ackermann reported the first photo-induced copper-catalyzed C–H arylation and C–H chalcogenation of heterocycles in the absence of additional photocatalysts [24, 25]. Subsequently, Rueping and Sundararaju disclosed an elegant cobalt-catalyzed alkyne annulation with the aid of Na₂Eosin Y photosensitizer under visible light irradiation [26].

In spite of this considerable progress, photo-induced organometallic C–H activation was thus far largely limited to soluble catalysts. Homogeneous catalysis is generally considered to be inadequate for the reuse of catalysts and often leads to undesired trace-metal impurities in the target products. In stark contrast, heterogeneous catalysis allows for the recovery of the catalyst, which increases recyclability as well as reusability in C–H activation [27]. In addition, the concept of immobilized catalysts has recently been recognized for thermal direct transformations, with a focus on heterogenized noble metals, such as palladium-, rhodium-, and iridium-catalyzed thermal transformations [28–32]. Unlike classical heterogeneous catalysts, immobilized heterogeneous catalysts consist of an inorganic support and a homogeneous catalyst, which is covalently anchored by an organic linker. Thus, these immobilized catalysts provide an avenue for tailorable and recyclable catalysis. Indeed, the heterogenized

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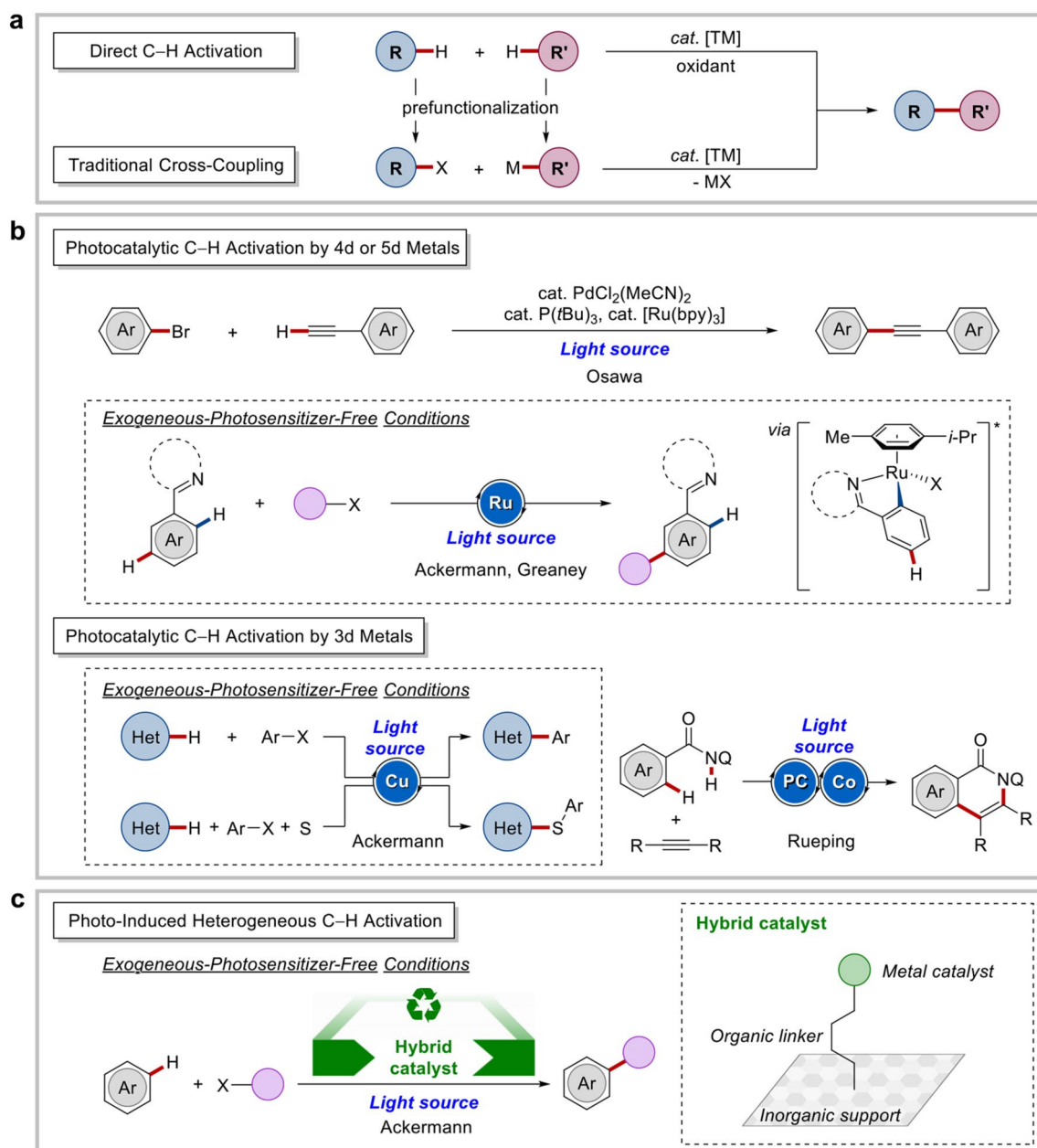


Fig. 1 Photo-induced heterogeneous C–H activation without exogenous photocatalysts. **a** Conventional cross-coupling reactions and direct C–H activation. **b** Homogeneous photo-induced C–H activation. **c** Heterogeneous photocatalytic approach in C–H activation

homogeneous catalysts—often referred to as hybrid catalysts—have been very recently utilized for photocatalytic C–H activation (Fig. 1c), which will be discussed within this Account.

Since the detailed aspects of homogeneous and heterogeneous metal-catalyzed C–H activation have previously been reviewed [4, 5, 22, 27], the scope of this Account includes photo-induced organometallic C–H activation by means of recyclable, covalently bound metal catalysts under exogenous-photocatalyst-free conditions until September 2021, excluding outer-sphere C–H functionalization processes.

2 Photo-induced distal C–H activation by heterogeneous ruthenium catalyst

While a wealth of *ortho*-selective C–H activations of arenes has been reported, methods for remote *meta*- or *para*-selective C–H functionalizations remain underdeveloped. Hence, only few strategies have thus far been realized for distal functionalizations by the use of expensive iridium and palladium catalysts [33–35]. In sharp contrast, *meta*-C–H functionalizations have been realized by ruthenium catalysis. The ruthenium-catalyzed

meta-C–H functionalization was observed by Ackermann (Fig. 2) in 2011 during studies on *ortho*-selective alkylation of phenyl pyridine **1** using carboxylate assistance [36]. This reaction proceeds through initial cyclometalation and ligand exchange generating complex **6** [37]. Subsequent single-electron-transfer (SET) with alkyl halide **2** yields ruthenium(III) species **7**, which then delivers intermediate **9**. Subsequent rearomatization and protodemetalation delivers the *meta*-substituted product **4**, and regenerates the active catalyst. Afterward, numerous studies for distal C–H functionalizations by ruthenium catalysis have subsequently been reported [38–41]. Here, computational studies, such as Fukui radical indices [42, 43] or molecular orbital analysis [44], unraveled key mechanistic insights into ruthenium-catalyzed *meta*-C–H functionalizations.

Recently, the group of Ackermann disclosed photo-induced remote *meta*-C–H functionalization under exogenous-photosensitizer-free conditions (Fig. 3) [16]. In this strategy, the cyclometalated ruthenium complex **14** which generated from the substrate **11** is excited by visible light irradiation, giving intermediate **15**, which is followed by SET to the alkyl halide **12**. Thereby, ruthenium complex **16** and alkyl radical **17** are generated. Next, the alkyl radical **17** attacks the aromatic moiety at the position *para* to

ruthenium, forming intermediate **18**, which undergoes intramolecular SET and subsequent rearomatization to provide ruthenacycle **20**. Thereafter, a protodemetalation process affords the desired *meta*-functionalized arene **13**. In the photo-induced conditions, elevated reaction temperatures can be avoided for distal C–H activation.

Inspired by their previous studies, in 2020, the group of Ackermann introduced the polymer-based immobilized ruthenium catalyst **23** for site-selective photo-induced C–H activation of arenes **21** under exceedingly mild reaction conditions, affording *meta*-functionalized arenes **24** (Fig. 4) [45]. Based on detailed mechanistic insights [42, 43], an immobilized phosphine was identified as being optimal for effective *meta*-C–H alkylations [45]. It is noteworthy that biomass-derived 2-MeTHF was identified to be the optimal reaction medium [46], while additional exogenous photocatalysts were not required for this distal transformation. In this study, various heteroarenes, such as pyridine, purine, and oxazoline, efficiently afforded *meta*-decorated arenes **24a–c** and the heterogenized ruthenium catalyst **23** was found to be reusable for the photo-induced *meta*-C–H alkylation.

The established hybrid ruthenium catalysis was also applicable to thermal reaction conditions (Fig. 5). Thereby, the heterogenized ruthenium catalyst **23** featured excellent

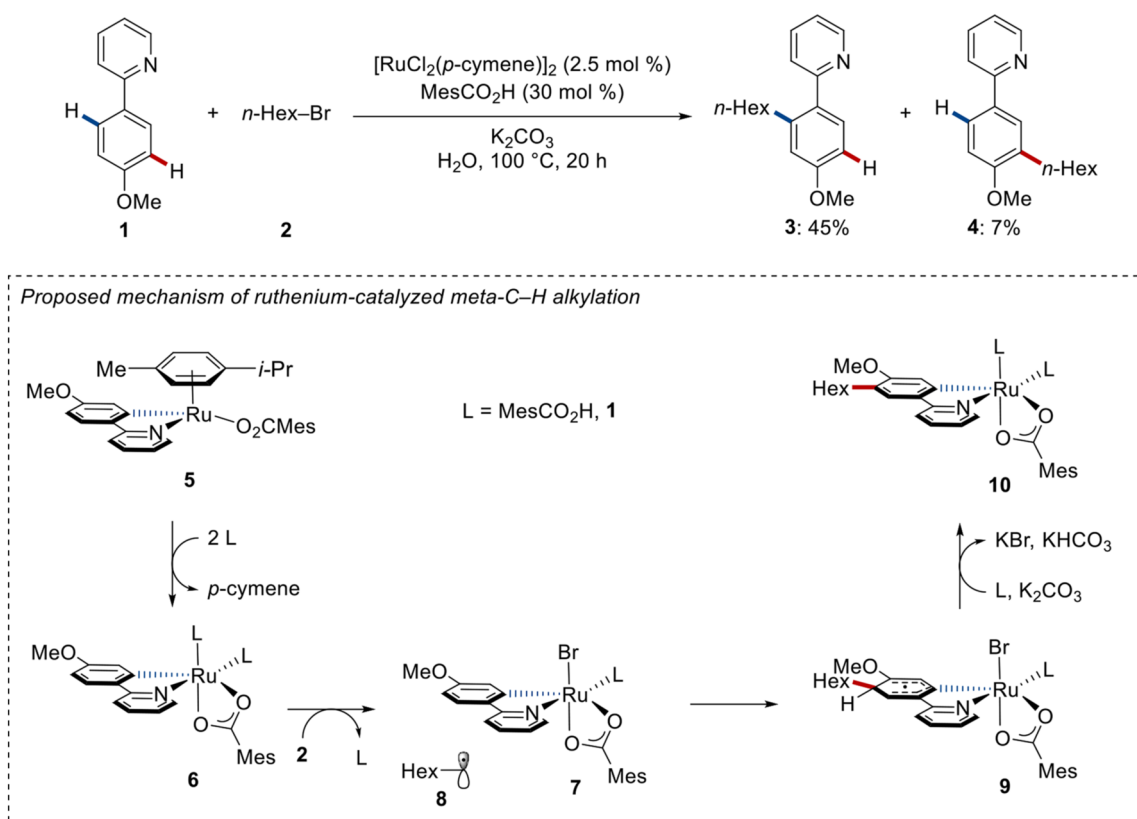


Fig. 2 The first observation of remote *meta*-C–H functionalization

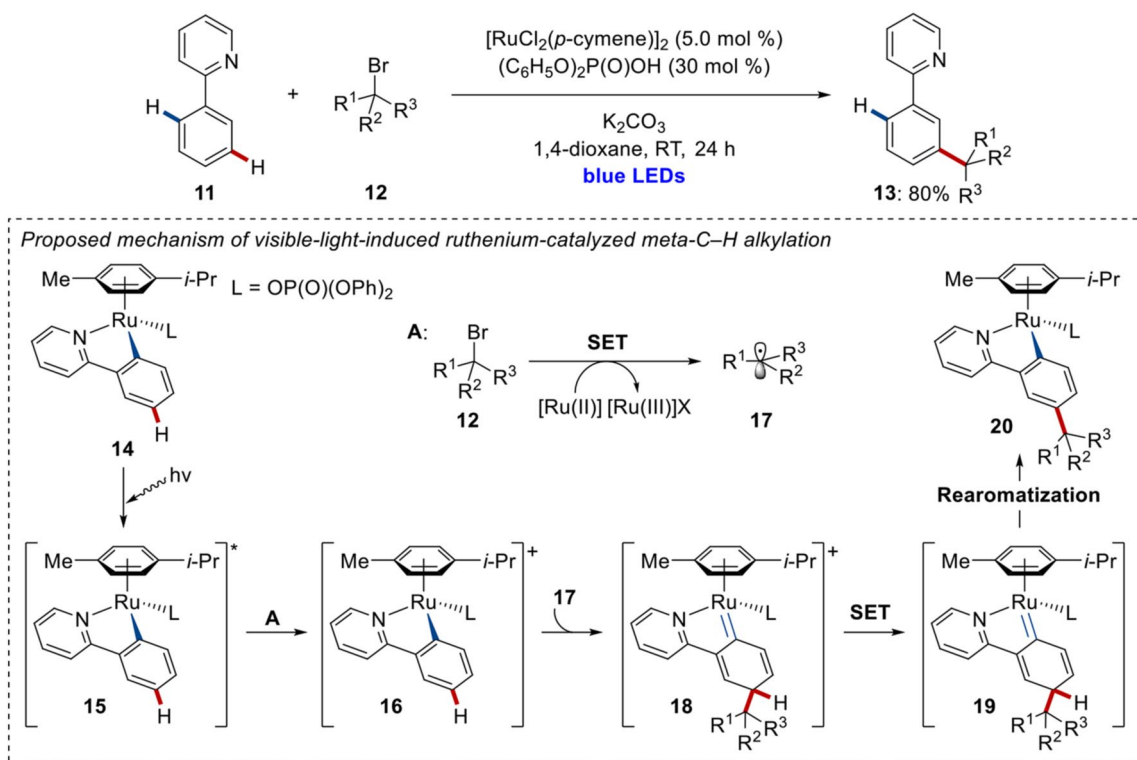


Fig. 3 Visible-light-induced ruthenium-catalyzed *meta*-C–H alkylation

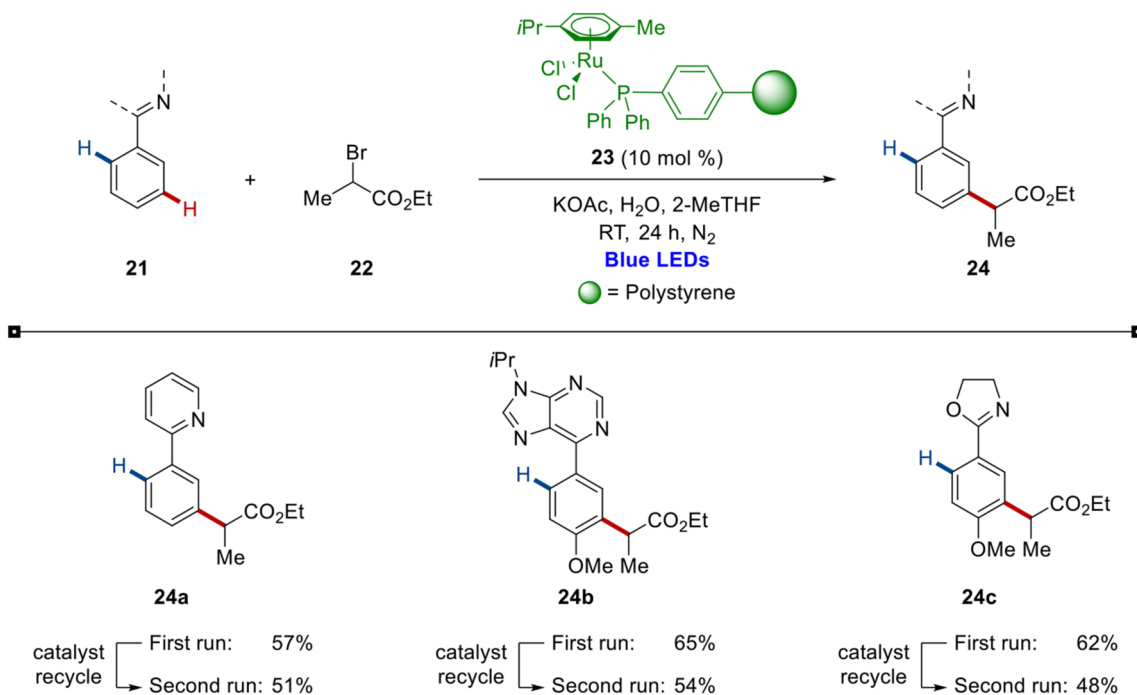
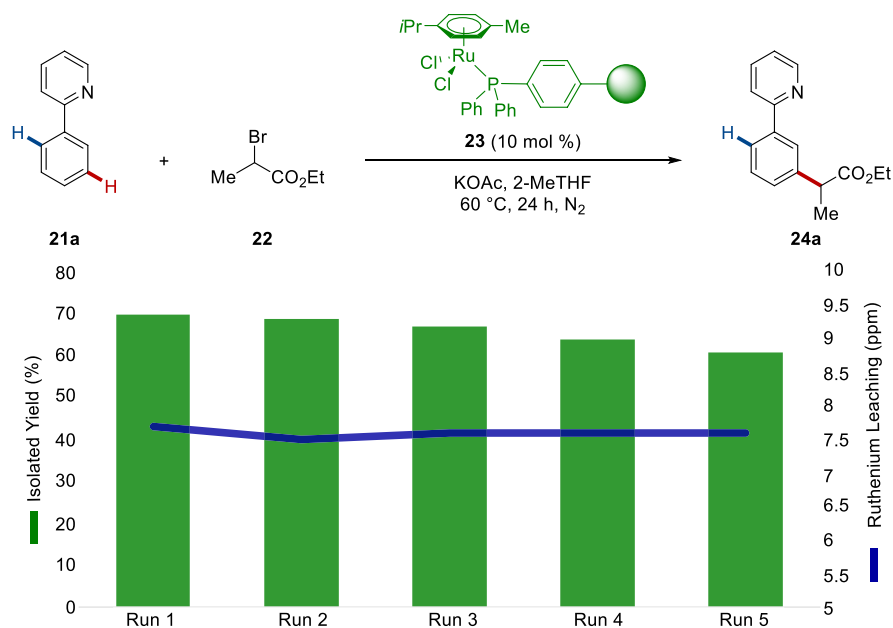


Fig. 4 Photo-induced *meta*-C–H alkylation by recyclable hybrid ruthenium catalyst

Fig. 5 Highly reusable hybrid ruthenium catalyst for distal C–H functionalization



recyclability without significant loss of catalytic efficacy, enabling versatile access to *meta*-C–H alkylated arene **24a**. Importantly, less than 8 ppm of ruthenium was detected by detailed inductively coupled plasma-optical emission spectrometry (ICP-OES) studies of the reaction mixture, reflecting negligible leaching of the transition metal. Notably, the heterogeneity of the covalently bound ruthenium catalyst **23** was verified by hot-filtration, poison, and three-phase tests, while the spectroscopic and microscopic characterization of the catalyst, along with detailed experimental and computational mechanistic studies, provided strong support for high position-selectivity enabled by the reusable hybrid catalyst **23**.

3 Photo-induced heterogeneous copper-catalyzed C–H activation

Copper complexes are easily accessible and versatile 3d metal catalysts for molecular assembly, because of copper's natural abundance, low toxicity, and wide range of oxidation states. Thus, copper catalysts have largely been exploited for new bond formation, such as C–C or C–heteroatom bonds [47–49]. In contrast to early examples of copper-catalyzed C–H functionalizations through SET mechanisms, copper has in recent years emerged as a viable metal for C–H activation through organometallic C–Cu intermediates [50–55]. Particularly, copper-catalyzed C–H arylations have been extensively investigated with notable contributions by Dauulis [56], Miura [57], and Ackermann [58].

Despite these major advances, copper-catalyzed C–H activation with aryl halides were largely restricted by their

harsh reaction conditions with reaction temperatures commonly ranging from 120 to 160 °C. However, the emergence of photocatalysis allowed for various sustainable organic syntheses under mild conditions, which further enabled photo-induced copper-catalyzed C–H activation. In 2016, the Ackermann group thus disclosed the first photo-induced copper-catalyzed C–H arylations of heterocycles **25** under exceedingly mild reaction conditions, providing C2-arylated benzothiazoles **27** (Fig. 6a) [24]. Here, abundant and inexpensive copper iodide allowed for the direct arylation of azoles under UV- or blue-light-irradiation. This photocatalytic C–H activation manifold proved later amenable to the copper-catalyzed C–H chalcogenation of heterocycles **25** with elemental sulfur and selenium, affording the chalcogenated products **28** or **29** (Fig. 6b) [25].

Encouraged by our reports, Ackermann and coworkers developed a novel heterogenized copper catalyst **31**, enabling the immobilization of copper iodide onto the bipyridyl group containing SBA-15 silica support **30** (Fig. 7) [59]. The chelating *N,N*-coordination motif is frequently found in homogenous C–H arylation copper catalysts [22].

This silica-based hybrid copper catalyst **31** was exploited for C–H arylation of azoles (**32** and **33**) with ample substrate scope (Fig. 8a). Interestingly, the sole use of copper iodide fell short in efficiently delivering the desired arylated product **34a**, while the developed reaction protocols provided an easy and sustainable access to the alkaloid texamine (**35d**) with high levels of site selectivity at the C2 position. Indeed, the broadly applicable covalently bound copper photocatalysis was extended to feature *N*-methyl benzimidazole **36** as a viable substrate under slightly modified reaction conditions, significantly

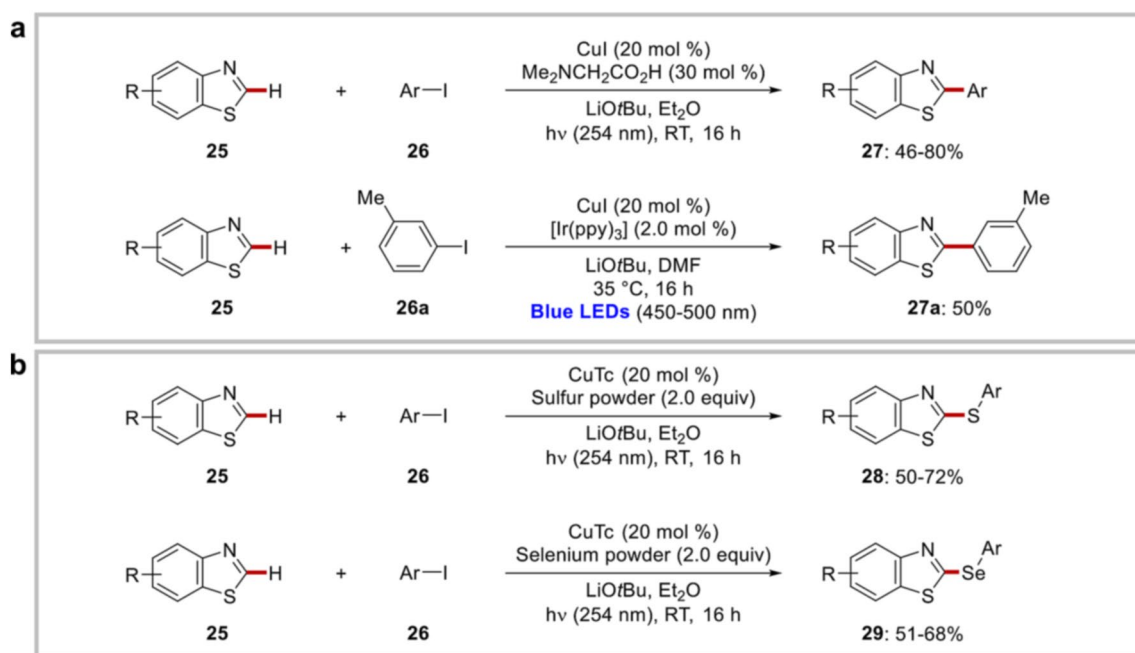
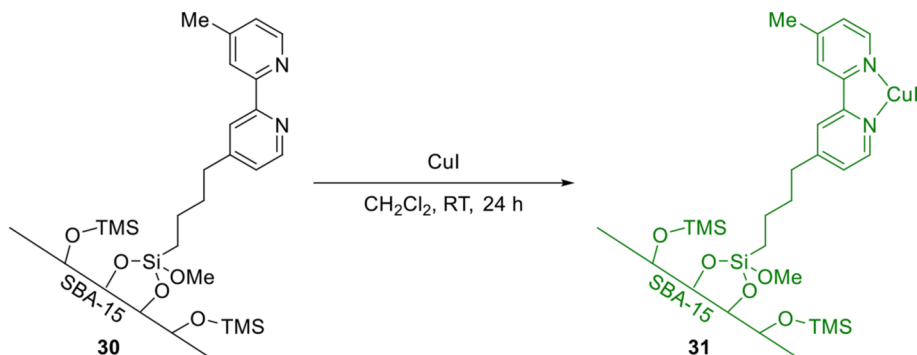


Fig. 6 The emergence of photo-induced copper-catalyzed C–H activation. **a** C–H arylation by cupraphotocatalysis. **b** Copper-catalyzed photo-catalytic C–H chalcogenations

Fig. 7 Preparation of hybrid copper catalyst



widening the functional group tolerance to include sensitive ketones and esters (Fig. 8b). More importantly, cost-effective aryl bromides **40** were also identified as suitable substrates, reflecting the robustness of hybrid copper catalysis in photochemical C–H activation (Fig. 8c).

It is particularly noteworthy that the immobilized copper catalyst **31** was indeed recyclable, as shown by the reuse tests, along with careful ICP-OES analysis (Fig. 9). Furthermore, while detailed heterogeneity studies highlighted the heterogeneous nature of the heterogeneous copper catalyst **31** in the photo-induced C–H activation, analysis by high-resolution transmission electron microscopy (HRTEM) and X-ray photoelectron spectroscopy (XPS) indicated the outstanding robustness and stability of the novel immobilized copper catalyst **31**.

4 Summary and outlook

During the last decades, photocatalysis has undergone renaissance, and photochemical reactions have been identified as an increasingly viable toolbox in molecular sciences. Thus, photocatalysis for C–H activation has surfaced as a sustainable platform in modern synthesis, allowing for innovative chemical transformations. In sharp contrast, photocatalytic C–H activations using a tailorable heterogeneous catalysts have until recently proven elusive. Herein, we have described our recent progress in photo-induced C–H activation by recyclable covalently bound metal catalysts. First, a polymer-based hybrid ruthenium catalyst enabled photocatalytic distal *meta*-C–H alkylation

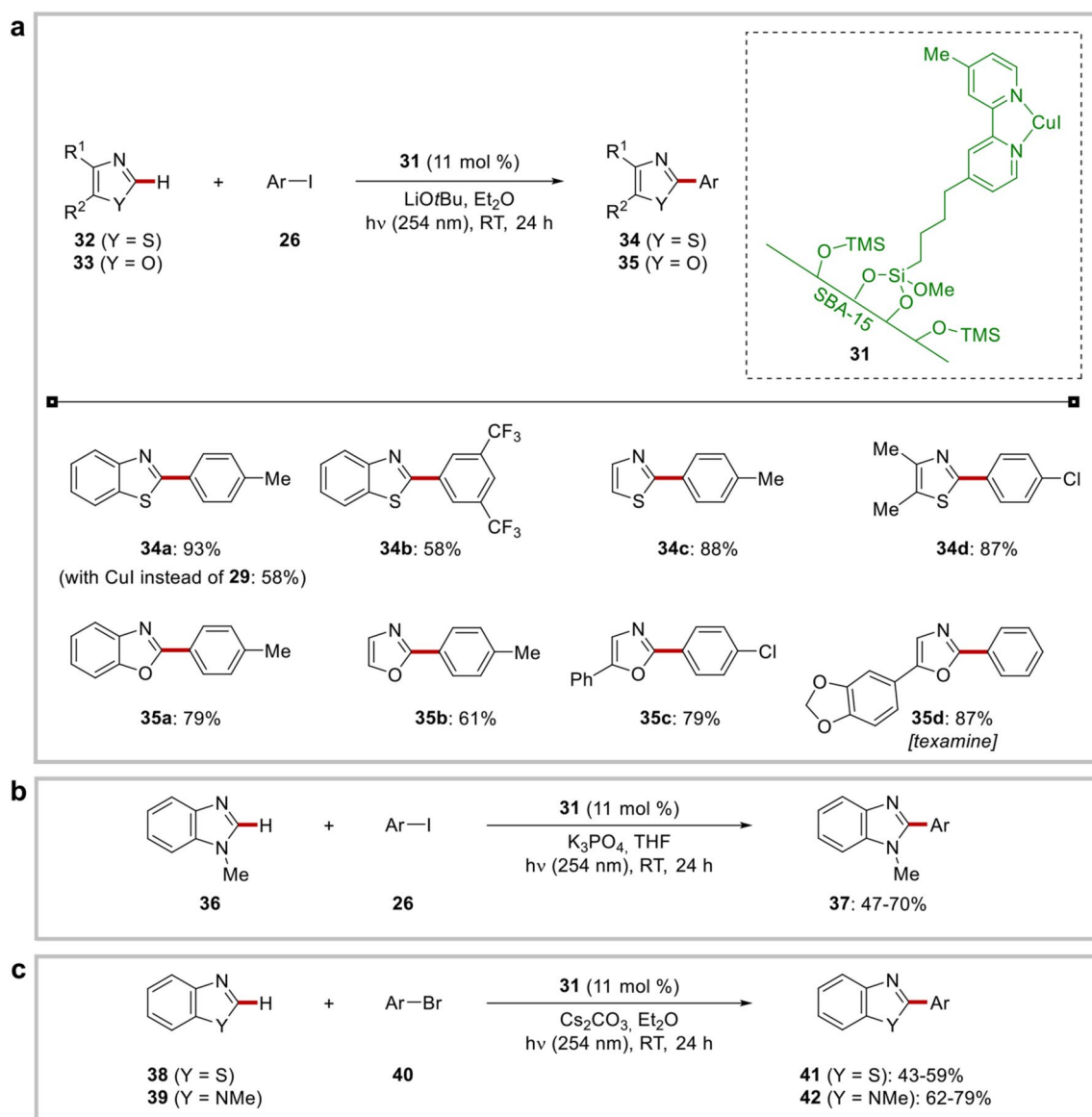


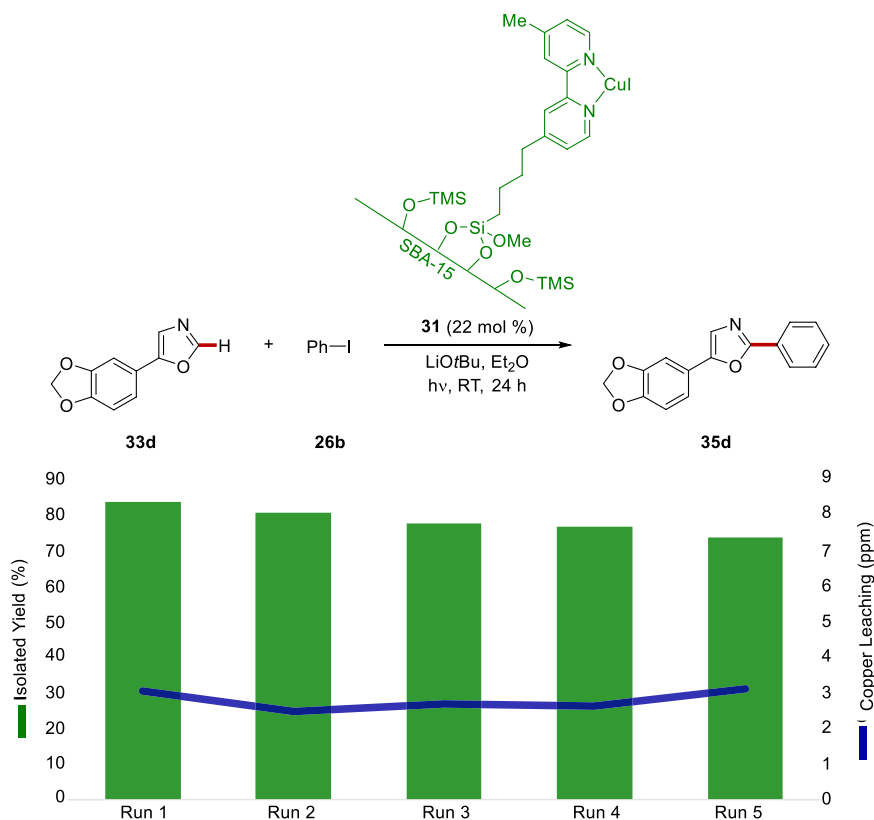
Fig. 8 Photo-induced heterogeneous copper catalysis for C–H arylations. **a** Photocatalytic C–H activation by a versatile immobilized copper catalyst. **b** Hybrid copper catalysis enabling photo-induced

C–H arylation of imidazole-based heterocycles. **c** Robust hybrid copper catalysis for photo-induced C–H arylation with cost-effective aryl bromides **40**

in a reusable fashion with ample scope. Second, the silica-based hybrid copper catalyst allowed for light-induced C–H arylations of various heterocycles, featuring robust recyclability without significant loss of catalytic efficacy. Given the sustainable nature of photo-induced C–H activation with reusable transition metal catalysts, we strongly believe that further exciting advances can be envisaged in

this research arena, which will guide recyclable and environmentally sound methodologies for molecular assembly-line synthesis. These should require multidisciplinary collaborations, including the exploration of alternative metals [60], the engineering of innovative materials [61, 62], electrocatalysis [63–66], and asymmetric C–H transformations [67, 68], among others.

Fig. 9 Recyclability and metal leaching of the hybrid copper catalyst for photo-induced C–H arylation



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Declarations

Conflict of interest The authors declare no competing financial interests.

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